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13. ABSTRACT *(Maximum 200 Words)*

This is the final report on a clinical trial of breast cancer patients designed to test the hypothesis that administering an antidepressant medication during chemotherapy treatment would prevent or alleviate the development of treatment-induced fatigue. We conducted a randomized, double-blind, placebo-controlled clinical trial with 124 breast cancer patients who were studied for up to four successive chemotherapy treatments. Patients were randomized to take the antidepressant paroxetine (Paxil®) or placebo once a day during the trial. They completed measures of fatigue and depression on the 7th day following each of the four chemotherapy cycles. Patient motion was assessed as a concomitant measure of fatigue by ambulatory electronic monitoring during the second and fourth assessments. Contrary to expectations, our findings showed that paroxetine was not helpful in reducing or preventing fatigue in cancer patients undergoing chemotherapy. They did, however, show that paroxetine can reduce depression in cancer patients undergoing chemotherapy, suggesting that depression and fatigue are differentially affected by an SSRI known to modulate brain 5-HT levels. Our findings also provide evidence that the physiologic process of circadian rhythm disruption is involved in the psychological experience of fatigue and depression in cancer patients.

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INTRODUCTION

This is the final report on a clinical trial of breast cancer patients designed to test the hypothesis that administering an antidepressant medication during chemotherapy treatment would prevent or alleviate the development of treatment-induced fatigue. We conducted a randomized, double-blind, placebo-controlled clinical trial with 124 breast cancer patients who were studied for up to four successive chemotherapy treatments. Patients were randomized to take the antidepressant paroxetine (Paxil®) or placebo once a day during the trial. They completed measures of fatigue (the Fatigue Symptom Checklist, the Profile of Mood States (POMS) fatigue subscale, and the Multidimensional Assessment of Fatigue) and depression (POMS depression subscale, Hamilton Depression Inventory, and the Center for Epidemiological Studies Depression Scale) on the 7th day following each of the four chemotherapy cycles. Patient motion was assessed as a concomitant measure of fatigue by ambulatory electronic monitoring during the second and fourth assessments. Analyses were conducted to examine the effectiveness of the intervention, the role of depression in the development of fatigue, and the temporal interrelationships among fatigue, circadian rhythms and depression. Patient blood samples were drawn at the second and fourth on-study treatments and were analyzed for TNF-α levels. Future analyses will examine the relationship between these levels and the other study variables.

BODY

Purpose

Fatigue is the most commonly reported treatment side effect of chemotherapy for breast cancer. Fatigue has been found to be up to seven times more prevalent in cancer patients than in the general population.[1] It is frequently reported to begin with treatment, continue through the course of chemotherapy, and often persist following treatment completion. We studied 1048 consecutive outpatients treated solely with chemotherapy over five successive treatments and found that 81% of women with breast cancer reported fatigue. It was the most common side effect the women experienced. The adverse effects of fatigue are frequently underestimated, and, thus, go untreated.[2,3] In addition to being pervasive, persistent, debilitating and discouraging, chemotherapy treatment-induced fatigue may have serious consequences for the breast cancer patient's quality of life and ability to actively participate in their treatment.

Fatigue can affect compliance with potentially curative treatment for breast cancer. Fatigue is a common reason given by cancer patients who refuse to enter experimental protocols.[4] Some women undergoing chemotherapy for breast cancer have been found to experience a loss of attention capacity on neurocognitive tests during treatment.[5,6] This impairment may reduce a patient's ability to make decisions regarding her treatment options and their effect on her well-being.[7] Since fatigue can challenge a patient's ability to complete recommended treatment on the optimal schedule,[8] it is apparent that fatigue may indeed reduce a woman's chance for curative cancer therapy.

Fatigue interferes with a patient's quality of life. Treatment-induced fatigue can quite significantly reduce a patient's participation in leisure activities, ability to sustain meaningful relationships with spouse and family, and capacity to work. Patients may be placed in a

dependent posture of having to depend on others for home management, transportation and even simple self care activities, such as preparing food or bathing.

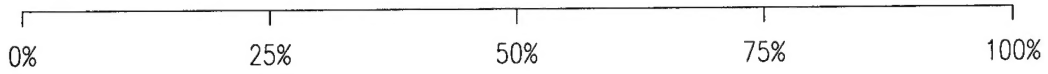
There has been little systematic research on the pattern of development, etiology, or treatment of fatigue during chemotherapy treatment for breast cancer. An effective treatment for chemotherapy-induced fatigue in women with breast cancer holds promise for increasing not only quality of life but also compliance with treatment, and, thus, prognosis for cure. A better understanding of potential mechanisms of chemotherapy-induced fatigue could lead to improved pharmacological and perhaps behavioral control of this debilitating symptom commonly experienced by women during treatment for breast cancer.

Our research will address three technical objectives: 1) to assess if an antidepressant drug can attenuate or prevent the development of fatigue in women during chemotherapy treatment for breast cancer; 2) to systematically investigate the role played by depression, both as a categorical diagnosis and a dimensional construct, in the development of fatigue during chemotherapy treatment, and 3) to extend pilot data that show an association between the cytokine TNF-α and patient-reported fatigue.

Background

Fatigue is a very common and troublesome side effect experienced by women during chemotherapy treatment for breast cancer. This prevalent and important problem has been largely overlooked. There is little systematic controlled research on either the etiology or treatment of fatigue during treatment for breast cancer. In a recent review, Winningham et al[2] summarized the following: "Despite its frequent occurrence, fatigue associated with chemotherapy is poorly understood" (pp 27). A sizable number of potential variables have been hypothesized to be involved in the development of fatigue; very few have been experimentally investigated. Only a select few can be included in any study without unduly burdening patients. Past studies are supported by our pilot data which suggests that psychological depression and the cytokine TNF-α are involved in the development of chemotherapy-induced fatigue.

Fatigue is the most common symptom experienced by patients with cancer.[10-12] It is up to seven times more prevalent in cancer patients than in the general population.[1] Cancer patients frequently report that fatigue begins with treatment, continues during the course of chemotherapy, and declines somewhat but persists at a higher-than-baseline rate after treatment is over.[13-15] The figure on the next page summarizes the percentage of patients in seven studies[16-22] (with a variety of diagnoses receiving various chemotherapy treatments) who reported fatigue.



Our data from a series of 1048 consecutive outpatients treated solely with chemotherapy for histologically verified oncologic disease at the four hospitals of the University of Rochester Cancer Center and at 15 geographically diverse private practice sites that form a part of our affiliated network of Community Clinical Oncology Program (CCOP) members further support the findings shown above. Patients completed a standardized checklist of 31 common treatment side effects based on the Boston System for Adverse Side Effects. Fatigue was reported by 70% of all patients and 81% of women with breast cancer.[23] No relationship was found between the reporting of fatigue and the utilization or effectiveness of the antiemetic regimen ($p>.05$), suggesting that fatigue is not a side effect of antiemetic drugs. Age was related to fatigue and a significantly higher proportion of patients (74%) below the sample median age of 53 reported fatigue compared to 64% of patients above the median age ($p<.05$). In a smaller series of patients, Piper [(29)] found no association between fatigue and age.

The high prevalence of fatigue has been further supported in a second, separate randomized clinical trial of ours where 83% of the 142 patients currently entered have reported fatigue by their second chemotherapy treatment. Unfortunately, fatigue is often accepted as a "normal" part of cancer treatment by medical staff. Its adverse effects are frequently underestimated,[19] and, thus, go untreated. In addition to being pervasive, persistent, debilitating and discouraging,[18] chemotherapy treatment-induced fatigue may have serious consequences for breast cancer patients' quality of life and ability to actively participate in their treatment.[2,8]

Fatigue interferes significantly with a patient's quality of life in many areas.[24-26] It can reduce breast cancer patients' ability to participate in leisure activities,[27] their capacity to sustain meaningful relationships and activities with their families,[28] to work, and to engage in social and other activities during and after treatment.[25,5] It also places them in a position of depending on others for home management, transportation, and even simple self-care activities, such as preparing food or bathing.[5,7] This change in daily activity and self-sufficiency may be demoralizing and discouraging. Furthermore, in addition to the activities in which fatigued patients are unable to participate, patients frequently must engage in unwanted activities, such as lying down or taking naps in an attempt to cope with their fatigue.[29]

Fatigue is a common reason given by cancer patients who refuse to enter experimental protocols.[4] Cimprich[6] found that women with breast cancer undergoing chemotherapy experienced a significant loss in attention capacity on neurocognitive tests during treatment. This impairment may reduce a

patient's ability to make decisions regarding her treatment options and their effect on her well-being.[7] When added to the fact that fatigue also often challenges a patient's ability to complete recommended treatment on the optimal schedule,[8,9] the potential that fatigue has to reduce a woman's chance for curative treatment is apparent.

Although fatigue is a nearly ubiquitous symptom associated with cancer and its treatment, no single definition of fatigue has gained complete acceptance.[2,30] Fatigue is seen as a different concept than tiredness, which is typically expected at a certain time of day or after activity, and which disappears after a short rest or a good night's sleep. In contrast, fatigue is typically reported by breast cancer patients to be an unusual, excessive, and pervasive whole-body experience which is disproportionate or unrelated to activity or exertion and is furthermore not helped by rest or sleep.[29] Fatigue is commonly viewed as a multidimensional construct (similar to pain[31]) which has clinical characteristics that can be conceptualized and measured in several dimensions. Based on this rationale, we will assess fatigue with both subjective and objective measures.

Definitive simple causal relationships between single factors and fatigue outcomes have not been found.[1,2,3,10,32] The likelihood that a combination of mechanisms is involved in the development of fatigue is consistent with most current models, such as the Aistairs Organizing Framework,[33] Piper's Integrated Fatigue Model (IFM),[29] and Winningham's Psychobiologic-Entropy Hypothesis (PEH).[9] The relationship between chemotherapy treatment and fatigue is likely to involve general physiological processes, specific factors related to treatment, and the influence of depressive disorders.

Data reviewed below show that fatigue is strongly associated with depression.[14,33,34] Fatigue is one of the diagnostic criteria of DSM IV depressive disorders, including major depression and dysthymia.[35] Chen found in a cross-sectional study that adults who experience depression are five to seven times as likely to feel fatigued[1] than adults who do not. In medical patients, depression has been strongly associated with fatigue experienced by patients in intensive care[36] and with fatigue in patients undergoing ambulatory care.[11]

Results from several converging areas of research support a role for depression as a major factor in the etiology of fatigue commonly found in chemotherapy patients: 1) there is a high frequency of depression in cancer patients undergoing chemotherapy, 2) several studies have found a significant positive correlation between depression and treatment induced fatigue. and 3) an intervention study showed that reducing depression decreased patient symptoms of fatigue. The first two areas are detailed below. The intervention study is described as part of our pilot data in the section that follows.

There is a high frequency of depression in cancer patients. The table below shows the percentage of cancer patients undergoing treatment and experiencing depression in five studies[7,20,37,38,39] that used a structured clinical interview to classify depression by DSM-IIIR criteria for depression. Depression was found in 40% to 82% of patients, with a mean percentage of patients with depression (weighted by the number of people per study) of 58%.

Table 1. Percentage of Cancer Patients Reporting Depression in Five Studies (N=311)

	N	Frequency
Mitchell & Glickman[39]	50	82%
Peck & Boland[37]	50	74%
Devlen et al[7]	120	40%
Nerenz et al[20]	61	61%
Kubricht[38]	30	56%
Mean Weighted Incidence		**58%**

There is a significant, positive correlation between depression and treatment-induced fatigue. Blesch et al[14] found a correlation of r=0.46 between depressed mood and fatigue in 77 lung and breast cancer patients receiving chemotherapy or radiation treatment. Piper et al[40] also found a significant association (r=0.49, p<.01) between depressed mood and fatigue in a sample of breast and lung cancer patients. Jamar[16] found a significant correlation (r=0.94) between fatigue and depression in women with ovarian cancer undergoing chemotherapy.

In a study of women with breast cancer undergoing six cycles of chemotherapy, Piper[29] reported that out of all variables measured, depression (measured by the Profile of Mood States: POMS depression subscale) had the largest and most consistent association with fatigue following each chemotherapy cycle. Depending on the treatment cycle, the correlation of depression with fatigue ranged from r=0.50 to r=0.80. Depression accounted for 10% to 64% of the unique variance in the number of fatigue symptoms reported concurrently and 7% to 58% of the unique variance in the intensity of fatigue concurrently reported on the Fatigue Symptom Checklist (FSCL).[41]

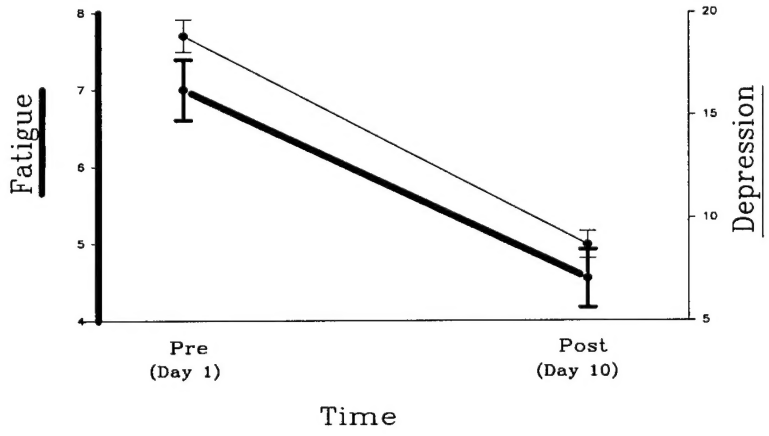
Fatigue reported after patients' second chemotherapy treatment was significantly related to their ratings of depression following their first chemotherapy treatment in a previous study where 451 consecutive cancer patients have been studied to date. Patients reporting fatigue had mean depression values on the Symptom Checklist-90 (SCL-90) close to one standard deviation above those of patients without reported fatigue (M=58.7 +/- 8.8 vs. M=49.1 +/- 10.4; t=9.6; p<0.01). They also had significantly more previous depressive affect on the Profile of Mood States (POMS; t=6.1; p<.01). The significant relationship was also found in subgroup analyses of breast cancer patients.[23]

Psychological depression as measured by either symptoms (SCL-90) or mood (POMS) appears related to subsequent chemotherapy-induced fatigue. A finding that patient-reported depression correlated with subsequent patient reported fatigue suggests, but does not prove, a causal link. The proposed study will analyze repeated measures of depression and fatigue by cross-lagged statistical procedures described later. Current pilot data support an association; research proposed here will begin a further systematic examination of this association.

A previously reported clinical trial in which our research team participated with the Psychosocial Collaborative Oncology Group, studied a sample of cancer patients for whom alprazolam (Xanax®) was administered over a ten-day period[42] to reduce depression (measured by the Hamilton Depression Rating Scale). A post-hoc re-analysis of data from this study shows that fatigue was reduced along with depression.

Since the trial was not designed to assess fatigue, no specific fatigue measure was used. A measure of fatigue was constructed post-hoc from the various assessment instruments, not including the instruments used to measure depression. Five questions were selected that were quite similar to questions commonly found in existing scales that measure fatigue.[29,41,43,44] The following questions appeared to have face validity as measures of fatigue: "Feeling low on energy or slowed down;" "Feeling weak in parts of your body;" "Heavy feelings in your arms or legs;" "Feeling everything is an effort;" and "Slowness of thought and speech, impaired ability to concentrate, decreased motor activity." The five questions were found to be conceptually coherent with a Cronbach α internal consistency coefficient of 0.78.

Seventy-one patients receiving the drug alprazolam were originally reported to have a significant decrease ($p<.01$) in both self-report and clinician-rated depressive mood over a ten-day period. In the re-analysis, we also found a significant reduction on the post-hoc measure of fatigue over the ten-day study ($p<.001$). The significant decrease was also shown through an analysis of covariance with patients' depression scores used as a covariate. It appears that the antidepressant medication had an independent effect on the post-hoc measure of fatigue separate from its effect on depression. These results are shown in the figure below. The heavy solid line represents the re-analyzed data. Comparative data on the reduction of depression reported in the original manuscript are shown by the lighter line. While suggestive, findings using the post-hoc scale need to be viewed cautiously since the items were chosen for their face validity. Some questions may measure depression as well as fatigue.



Many variables have been hypothesized to be involved in the development of the fatigue found in women treated for breast cancer; few have been systematically investigated. Evidence that elevated production of cytokines is related to fatigue
comes from studies that have noted that marked fatigue can develop following therapeutic administration of cytokines including, TNF-α. TNF-α has also been associated with loss of muscle protein and decreased muscle contractility, which may result in increased feelings of fatigue and reduced physical activity.[2,32,45] Our recent pilot work supports this relationship. We

found that TNF-α levels fell significantly over three cycles of chemotherapy in five patients receiving the drug,Trental®, but not in ten patients receiving placebo (p=0.04) who were entered in a randomized clinical trial examining interventions for enhancing quality of life in cancer patients with recurrent disease. We also measured a TNF-α increase of 71% over, roughly, four months in a pilot series of six cancer patients with recurrent disease. Patient self-reported fatigue paralleled this increase. Over the same timeframe, scores on the POMS fatigue subscale increased 18%; fatigue items from the FACT-G measure of quality of life increased 17%; a visual analog scale scores of tiredness from the Edmonton Symptom Assessment Scale (ESAS) increased 43%; and values from a visual analog scale of the ESAS assessing drowsiness increased 78%.

The association of selective cytokine activation, including that of TNF-α, with fatigue in patients with Chronic Fatigue Syndrome as shown by the work of Borish[32] and colleagues; its known role in production of cancer-related anorexia and cachexia, and our preliminary evidence from an ongoing research study of the ability of Trental® to lower serum levels of the cytokine in patients receiving chemotherapy for metastatic malignancies provide a rationale for repeated measurement of serum levels of TNF-α in cancer patients receiving chemotherapy to further elucidate the etiology of fatigue in cancer patients undergoing treatment.

Technical Objectives

Specific Aim 1: To assess the degree to which an antidepressant drug can attenuate or prevent the development of patient fatigue during chemotherapy treatment for breast cancer.

Specific Aim 2: To systematically investigate the role played by depression, both as a categorical diagnosis and a dimensional construct, in the development of fatigue during chemotherapy treatment.

A secondary, exploratory aim was to extend pilot data that show an association between the cytokine Tumor Necrosis Factor (TNF-α) and fatigue, and their associations with depression in subjects with breast cancer.

Experimental Methods

Overview: Meaningful ideas that influence theory and clinical practice evolve over time from careful research that builds on past research findings, and, thus, strengthens their validity. This research is a step in that process. In developing this study, we have built on the literature and relevant work completed by other research teams, and on our own research background in studies with cancer patients in the areas of: 1) problem identification,[46] 2) psychosocial assessment techniques,[47] 3) methodology,[48]
4) evaluation of psychosocial and behavioral interventions to control treatment side effects, and
5) implementation of cancer control interventions.[49,50]

Design: Patients were stratified by chemotherapy treatment and randomized to either drug or placebo. Assessments were made seven days following chemotherapy administration over four successive chemotherapy treatments. Fatigue is generally reported by patients to be the most severe within the seven days following chemotherapy; the time of maximum chemotherapy effect on hematological parameters, such as hematocrit and hemoglobin. Anemia is frequently but not always associated with the presence of fatigue,[59] and Piper[29] did not find any association between fatigue and changes in hematocrit and hemoglobin levels following chemotherapy.

Nonetheless, illness-related clinical factors, such as hematocrit, hemoglobin, renal function, calcium, weight and other measures gathered as part of normal clinical procedures were recorded for potential use in exploratory, subgroup secondary analyses following the planned statistical analyses of data to address the two proposed and one exploratory aims.

The antidepressant or placebo was taken once a day from day seven following study treatment one until day 7 following study treatment four. Treatments were typically three to four weeks apart — thus, there was an adequate time for the antidepressant to reach a therapeutic level. While the data are not conclusive, fatigue may vary with type of chemotherapy treatment. The contradictory results found in previous studies of correlates of fatigue[52-55] may have been influenced by this variability. To help control this potential confound, patients were stratified based on chemotherapy treatment (Cyclophosphamide, Methotrexate, 5-Fluorouracil:CMF or Cyclophosphamide, Adriamycin, 5-Fluorouracil:CAF or other). The study ended at the assessment seven days after the fourth on-study chemotherapy treatment.

Proposed Sample: 130 Consecutive patients undergoing chemotherapy for breast cancer at any of the four affiliated hospitals of the URCC will be studied. Patients will be eligible if they are: undergoing chemotherapy treatment for histologically confirmed breast cancer; able to swallow medication; able to understand and speak English (since the standard assessment psychosocial instruments used here are only available in English versions); not presently taking psychotropic medication; not currently pregnant or nursing; and are currently scheduled for at least four cycles of chemotherapy (a typical treatment course with CMF or CAF is six cycles). Patients were excluded if they had: impaired renal, hepatic or cardiac function (as judged by their treating medical oncologist), history of seizures, history of mania, or are taking medications for which there are demonstrated interactions with Paxil®. Eligibility was checked during patient interviews and from patient records at each participating hospital.

Women and Minority Representation: Ten percent of the enrolled patients were Hispanic or Black. This proportion closely matches the minority composition (11%) of the city of Rochester and the surrounding 10-county area.

Drug Characteristics, Dosage and Administration: Patients randomized to the active arm of this study received a standard clinical dose of 20 mg per day of the antidepressant Paroxetine (Paxil®), a potent, selective inhibitor of serotonin reuptake that has little affinity for the catecholaminergic and histaminergic systems. Paroxetine has undergone extensive clinical testing. Caley and Weber[56] reviewed 14 randomized, double-blind trials involving 1425 outpatients with moderately severe depression. All 14 trials lasted 6 weeks. Four were placebo-

controlled and in the remainder an active drug arm was used with or without a placebo arm. The reviewers concluded that paroxetine is an effective treatment for moderately severe depression. In four trials, more than 50% of patients receiving paroxetine demonstrated a 50% or greater reduction in Hamilton Rating Scale for Depression (HRSD) scores over a six-week period compared to 23% of patients receiving placebo. In eight of the remaining ten trials, efficacy was comparable to or greater than that of the active drugs.

In another six-week randomized double blind trial comparing paroxetine with placebo in 167 patients with a major depressive episode, a significant difference in the total HRSD score was apparent between the two groups by the second week of treatment, and by the fourth week, there were significant differences in all variables that were measured. In addition, there was a significant difference in the sleep factor of the HRSD by the end of the first week of treatment, suggesting that paroxetine had less of an activating than a somnolent effect. Furthermore, more patients reported somnolence than nervousness, even when the frequency of these symptoms in patients taking placebo was accounted for. Improved sleep may act to decrease fatigue.[57] These findings suggest that paroxetine can produce a significant clinical effect during the active study period proposed in this study.

Paroxetine has been found to produce fewer side effects than first generation antidepressants, such as the tricyclic agents: amitriptyline (Elavil®), imipramine (Trofranil®), or the monoamine oxidase inhibitors: (phenelzine: Nardil®), or second generation agents, such as trazodone (Desyrel®). The few adverse effects on the central and autonomic nervous systems tend to be more transient than the antidepressants mentioned above and include: sedation, drowsiness, hypotension
and anticholinergic effects, such as dry mouth, constipation, blurred vision, and urinary retention.

Paroxetine does not impair motor performance, potentiate depressant effects of alcohol or other depressant medications, or disturb cardiac function. The drug is well absorbed from the gastrointestinal tract. Stable plasma concentrations are achieved within 4-14 days of being administered, and therapeutic effect is noted typically within four weeks. A mean terminal half-life of 24 hours permits once-daily dosing, which can also be an advantage in use with cancer patients who may often be taking other medication and are sometimes reluctant to take several more pills. It is metabolized primarily by the liver, and metabolites are pharmacologically inactive.

Paroxetine should not be given to patients being treated with monoamine oxidase inhibitors or other drugs that increase brain serotonin concentrations. Identical drug/placebo capsules will be prepared by our pharmacy. The placebo capsules are prepared with a filler that consists of 6 ml of D & C red dye #40 (100 mg/ml) added to each 100 gm of lactose, U.S.P.

Measures

Patients completed most instruments at home and mailed them back in stamped, self-addressed envelopes, or they will be picked up the next day when the motion monitor (explained below) was picked up at the patient's home. Instruments were administered one week following chemotherapy treatments, which is the time of greatest reported fatigue.[29] A reminder phone call

was made to patients on the 7th day after treatment ended when the measures were to be completed. Any questions they had were answered and the patient was encouraged to complete the measures that day.

Outcome Measures of Fatigue

- The Fatigue Symptom Checklist (FSCL)[41] Patients indicate the presence and intensity of each of 30 symptom items related to fatigue on a five-point scale. Reliability of the three subscales range from 0.77 (drowsiness and dullness) to 0.90 (projection of physical impairment); reliability for the total scores ranges from 0.92 to 0.94. Piper[29] found that the FSCL was completed a higher percentage of times than any other fatigue measure used in her study, including her own Piper Fatigue Scale. We asked ten patients to complete the Piper Fatigue Scale. The majority felt strongly it was "too confusing" and had "far too many questions." So, reluctantly, we decided not to use it.

- The Fatigue/Inertia (F/I) subscale of the Monopolar Profile of Mood States (POMS) Short Form measures fatigue as a mood through five items with an internal reliability ranging from 0.86 to 0.95 in six population samples.[58] We used it also in the pilot study of TNF-α presented above.

- The Revised Multidimensional Assessment of Fatigue (MAF)[59] measures four dimensions of fatigue (severity, distress, interference with daily living tasks, timing) through 16 questions. Internal consistency of 0.93 has been shown in 133 subjects, along with convergent and divergent validity.[60,61]

- Ambulatory Monitoring of Patient Activity[62] Patient motion averaged over selected time spans during a three-day period was used to assess fatigue. Use of this measure was prompted not only by the face validity of the measure (fatigued patients universally report marked reductions in activity), but also the fact that the original clinical diagnosis of Chronic Fatigue Syndrome contained a definition based on reductions in patient activity.[63] Activity was recorded by the mini-motion logger actigraph from Ambulatory Monitoring, Inc. This is an accelerometer and microprocessor with 32K of dedicated memory that is programmed through an interface device. Shown in the Figure below, it is approximately the size of a wrist watch.

A recent article[64] confirmed its reliability. We used it to sample patient activity six times a minute during the 6th, 7th and 8th days following chemotherapy administration for assessments two and four. Motion data will be analyzed by the approach developed by Oman.[65]

Measures of Depression

- Depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D[66] is a 20-item depression scale developed and validated for use with several populations. It uses a format similar to the Beck Depression Inventory, but with less emphasis on physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. It has been shown to reliably and validly measure depression in cancer populations.[67]

- Categorical diagnosis of depressed mood disorders. Severity of symptoms of depression was also measured using the Hamilton Depression Inventory (HDI).[68,69] This instrument comprises 23 items (or symptoms) that are evaluated using 38 questions. This is a recently developed paper and pencil version of the Hamilton Depression Rating Scale (HDRS) and measures the severity of symptoms of depression over the previous two weeks. Completion time is approximately ten minutes. The first 17 items correspond to those included in the original HDRS developed by Hamilton[70]; six additional items relate to symptoms of major depressive disorder and dysthymia.

- Depressive mood was measured with the Depression-Dejection subscale of the Profile of Mood States -- Short Version (POMS), which consists of five adjectives. It has been shown to be internally consistent (α=0.91), reliable and valid in a number of psychometric studies.[58]

- Tumor Necrosis Factor-α (TNF-α) serum levels will be measured by ELISA using a standard, commercially available kit from R and D Systems and the URCC laboratory currently running similar analyses for an ongoing study. The sensitivity of this method is 4.4-1000 pg/ml.

Sample Characteristics

Study subjects were patients at the University of Rochester Cancer Center and two affiliated hospitals. The Institutional Review Board of each participating site approved the protocol.

One hundred twenty-two women and two men consented to participate in the study. Twenty-two (18%) patients withdrew from the study prior to data collection from the second treatment. Ninety-six of the remaining 102 patients provided evaluable data following at least three treatments and are included in the analyses. The mean age of these 94 women and 2 men was 51.2 years (range = 31 to 79). Eighty-five (89%) of the patients were Caucasian. Thirty-six (37%) patients were receiving CMF therapy, 42 (44%) patients were receiving chemotherapy regimens containing cyclophosphamide and doxorubicin with or without fluorouracil, and 18 (19%) patients were receiving other chemotherapy regimens. Forty-five (47%) of these patients were assigned to the paroxetine condition and the remaining 51 (53%) to the placebo condition. The patients were all mobile and had an average Karnofsky Performance Status of 88.2 (range = 65 to

100). Using a CES-D score of 19 or greater to indicate depression, 14 (24%) patients in the placebo group and 14 (27%) in the paroxetine group were significantly depressed at baseline (25% combined).

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RESULTS

All measures of depression and fatigue were strongly correlated at both baseline and study outcome (all p's < 0.01) as has been found in previous studies of cancer patients undergoing treatment, confirming their co-existence in patients in this sample.

Depression: Using a CES-D score of 19 or greater to indicate depression, 14 (27%) patients in the placebo group and 14 (31%) in the paroxetine group were significantly depressed at baseline. By cycle four, only 4 (9%) of patients in the paroxetine group (all 45 patients remained on-study) had CES-D scores greater than 19 compared to 11 (24%) of those in the placebo group (46 of the original 51 patients were still on-study).

Analysis of covariance with the mean score of the CES-D (the primary measure of depression) from the 3rd and 4th treatments as the dependent variable, controlling for baseline CES-D, showed that paroxetine was more effective than placebo in reducing depression during chemotherapy (p = .03) (estimated marginal means: placebo = 12.5, SE = .84; Paxil = 9.7, SE = .90). Similarly structured analyses on the other two depression measures (POMS-DD and HDI) also showed a decrease in depression in the Paxil group compared to the placebo group, but these differences were not statistically significant (POMS-DD, p = .17, estimated marginal means: placebo = 2.09, SE = .25; Paxil = 1.59, SE = .26; HDI, p = .27, estimated marginal means: placebo = 11.1, SE = .64; Paxil = 10.0, SE = .68).

Fatigue: In contrast to its beneficial effect on symptoms of depression, paroxetine had neither beneficial nor detrimental effects on measured fatigue. Similar showed that treatment condition was not related to changes in fatigue (all ps > .5) (estimated marginal means: MAF, placebo = 23.3, SE = 1.2; Paxil = 22.3, SE = 1.3; FSCL, placebo = 48.1, SE = 1.7; Paxil = 46.6, SE = 1.8; POMS-FI, placebo = 7.0, SE = .50; Paxil = 7.1, SE = .53). Analyses using the actigraph measures of fatigue also showed no difference by treatment group. A complete description of the actigraph analyses are provided in the attached manuscript "Temporal interrelationships among fatigue, circadian rhythms and depression in breast cancer patients undergoing chemotherapy treatment".

Additional analyses on the effect of Paxil on fatigue and depression are provided in the attached abstracts and poster. Specifically, an abstract and its companion poster "Effect of an SSRI antidepressant on fatigue and depression in breast cancer patients treated with chemotherapy" utilized repeated measures ANOVA to examine the data with essentially similar results. We also reported that Paxil did not effect mood as measured by the POMS total score in an abstract entitled," An SSRI antidepressant reduced depression but not fatigue in ninety-six breast cancer patients".

Discussion

Paroxetine at a dose of 20 mg once daily had no effect on fatigue associated with receipt of chemotherapy in this randomized, placebo-controlled clinical trial of 96 patients with breast cancer. By contrast, paroxetine significantly reduced symptoms of depression. This provides evidence that the dose selected has biological activity upon the central serotinergic pathways involved in depression and mood. Although depression and fatigue were strongly correlated in our sample, only one of these symptoms was affected by the intervention.

We believe that the dosage and length of time patients took the drug was adequate to test the potential effectiveness of paroxetine in reducing fatigue. The dose used in this study, 20 mg once daily, is the generally recommended initial dose and was effective in relieving depression in previous randomized clinical trials conducted to determine the drug's efficacy.[56,57] These efficacy studies showed a significant drug effect within six weeks of patients' starting the medication. This study showed that symptoms of depression were reduced in the intervention group over the course of chemotherapy thus demonstrating that an adequate clinical dose was used. In this patient sample, each cycle of treatment was generally three to four weeks in length, so the typical patient was on medication for at least 9 weeks prior to final assessment. A recent study found that a lower dose of a similar drug, fluoxetine (Prozac®) than is often used (20 mg/day) was more effective than placebo in reducing symptoms of depression.[77] While we can not completely exclude the possibility that a higher dose of the SSRI might have a beneficial effect on fatigue, we view this possibility to be remote in view of the fact that not even a trend towards efficacy was noted at the dose given.

Somnolence, asthenia and fatigue have been reported as adverse effects by some patients treated with paroxetine. We believe it is unlikely that the drug contributed to patients' fatigue however, as there were not significant differences in measured levels of fatigue between the two study groups at any time point during the course of the study. If paroxetine was enhancing fatigue,

patients in the intervention group would be expected to report more fatigue at cycles three and four than those in the control group. They did not.

KEY RESEARCH ACCOMPLISHMENTS

- The study provides additional evidence that paroxetine can reduce depression in cancer patients undergoing chemotherapy.
- The data show that depression and fatigue are differentially affected by an SSRI known to modulate brain 5-HT levels.
- Contrary to expectations, our findings showed that paroxetine was not helpful in reducing or preventing fatigue in cancer patients undergoing chemotherapy.
- Our findings provide evidence that the physiologic process of circadian rhythm disruption is involved in the psychological experience of fatigue and depression in cancer patients.
- These results support the use of wrist actigraphy as a valid and reliable means of assessing fatigue in ongoing studies of patients receiving chemotherapy.

REPORTABLE OUTCOMES

1. **Abstract:** Hickok, J.T., Roscoe, J.A., Morrow, G.R., & Bushunow, P. (1998). Use of actigraphy to measure fatigue. Supportive Care in Cancer, 6, 186
2. **Abstract:** Hickok, J.T., Roscoe, J.A., Morrow, G.R., & Bushunow, P. (1998). Wrist actigraphy as a measure of fatigue. Proceedings of American Society of Clinical Oncology, 17, 60a, abstract #231.
3. **Abstract:** Morrow, G.R., Tian, L., Roscoe, J.A., Griggs, J.G., Hickok, J.T., Smith, B., Kramer, Z., & Kim, Y. (2000). The relationship between circadian rhythm and fatigue in breast cancer patients. Proceedings of the Society of Behavioral Medicine's Twenty-First Annual Meeting, 22, 2000 Supplement, S188
4. **Poster:** Morrow, G.R., Tian, L., Roscoe, J.A., Griggs, J.G., Hickok, J.T., Smith, B., Kramer, Z., & Kim, Y. (2000). The relationship between circadian rhythm and fatigue in breast cancer patients. Proceedings of the Society of Behavioral Medicine's Twenty-First Annual Meeting, 22, 2000 Supplement, S188
5. **Abstract:** Morrow, G.R., Roscoe, J.A., Hickok, J.T., & Matteson, S. (2001). Effect of an SSRI antidepressant on fatigue and depression in breast cancer patients treated with chemotherapy. Proceedings of the Society of Behavioral Medicine's Twenty-Second Annual Meeting

6. **Poster:** Morrow, G.R., Roscoe, J.A., Hickok, J.T., & Matteson, S. (2001). Effect of an SSRI antidepressant on fatigue and depression in breast cancer patients treated with chemotherapy. Proceedings of the Society of Behavioral Medicine's Twenty-Second Annual Meeting,

7. **Abstract:** Roscoe, J.A., Morrow, G.R., Bushunow, P., & Matteson, S. (2001). Circadian Rhythm, Fatigue and Depression in Breast Cancer Patients Receiving Chemotherapy. Proceedings American Society of Clinical Oncology 2001 Annual Meeting

8. **Abstract:** Morrow, G.R., Roscoe, J.A., Hickok, J.T., Smith, B., Qazi, R. (2001) An SSRI antidepressant reduced depression but not fatigue in ninety-six breast cancer patients. Abstract accepted for presentation at the Multinational Association of Supportive Care in Cancer International Symposium (2001)

9. **Manuscript in Preparation:** Roscoe, J.A., Morrow, G.R., Hickok, J.T., Bushunow, P., Matteson, S., Rakita, D., & Andrews, P.L.R., Circadian Rhythm, Fatigue and Depression in Breast Cancer Patients Receiving Chemotherapy. Supportive Care in Cancer

All publications are attached.

CONCLUSION

Study findings bear on both clinical and mechanistic issues. Clinically, paroxetine appears to be an effective treatment for depression in cancer patients undergoing chemotherapy. In terms of potential mechanisms, we hypothesized that fatigue and depression shared a final common neural pathway that involved serotonin. If so, an antidepressant of the selective serotonin re-uptake inhibitor (SSRI) class could likely mitigate both the fatigue and depression associated with cancer treatment by increasing the availability of 5-HT in the synaptic space. Study results are not consistent with this hypothesis. Rather, the data show that depression and fatigue are differentially affected by an SSRI known to modulate brain 5-HT levels. If there is a final common pathway to the expression of both fatigue and depression it is unlikely to involve central serotonin. Other pharmacological agents (e.g. psychostimulants)[78,79] and, perhaps non pharmacological interventions (e.g. cognitive behavioral therapy which has been effective in patients with chronic fatigue syndrome)[80] may be worthy of further controlled study.

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Appendix A
(Personnel)

1. Gary R. Morrow - Primary Investigator
2. Jane T. Hickok - Co-Investigator
3. Joseph A. Roscoe - Study Coordinator
4. Jacque Lindke - Data and Form Manager
5. Youngmee Kim - Data Analyst
6. Eva Galambos - Secretary
7. Ann Waiter - Secretary
8. Jill Sheflin - Data Entry
9. Jennifer Morrow - Data Entry
10. Kelly Kita – Office Assistant
11. Bruce Fenton – Lab Manager
12. Ivan Ding – Lab Technician
13. Brian Beauchamps – Lab Technician

Appendix B
(Publications)

1. **Abstract:** Hickok, J.T., Roscoe, J.A., Morrow, G.R., & Bushunow, P. (1998). Use of actigraphy to measure fatigue. Supportive Care in Cancer, 6, 186

2. **Abstract:** Hickok, J.T., Roscoe, J.A., Morrow, G.R., & Bushunow, P. (1998). Wrist actigraphy as a measure of fatigue. Proceedings of American Society of Clinical Oncology, 17, 60a, abstract #231.

3. **Abstract:** Morrow, G.R., Tian, L., Roscoe, J.A., Griggs, J.G., Hickok, J.T., Smith, B., Kramer, Z., & Kim, Y. (2000). The relationship between circadian rhythm and fatigue in breast cancer patients. Proceedings of the Society of Behavioral Medicine's Twenty-First Annual Meeting, 22, 2000 Supplement, S188

4. **Poster:** Morrow, G.R., Tian, L., Roscoe, J.A., Griggs, J.G., Hickok, J.T., Smith, B., Kramer, Z., & Kim, Y. (2000). The relationship between circadian rhythm and fatigue in breast cancer patients. Proceedings of the Society of Behavioral Medicine's Twenty-First Annual Meeting, 22, 2000 Supplement, S188

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9. **Manuscript in Preparation:** Roscoe, J.A., Morrow, G.R., Hickok, J.T., Bushunow, P., Matteson, S., Rakita, D., & Andrews, P.L.R., Circadian Rhythm, Fatigue and Depression in Breast Cancer Patients Receiving Chemotherapy. Supportive Care in Cancer

USE OF ACTIGRAPHY TO MEASURE FATIGUE

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Patients receiving chemotherapy for breast cancer and radiation for lung cancer were assessed *before, during* aid after treatment using the Profile of Mood States (POMS) and the Fatigue Symptom Checklist (FSC). We compared these measures of fatigue with the Mini-Motionlogger Actigraph (Ambulatory Monitoring, Inc., Ardsley, NY). Each day of the 40 Actigraph observations was divided into *intervals of time* most likely spent awake or in bed, and mean activity and percent sleep were determined for each interval. A lower percent of time spent sleeping during the in-bed period correlated with more fatigue symptoms, indicated by a higher mean total FSC score ($\underline{r} = -0.64; p < 0.01$), less vigor, indicated by the POMS Vigor Subscale score ($\underline{r} = -0.41$; $p < 0.01$), and greater total mood disturbance, measured by the total POMS score ($\underline{r} = -.52; p < 0.01$). Higher mean activity during the in-bed period, suggesting restless sleep or inability to sleep at night, also correlated with more fatigue symptoms ($\underline{r} = 0.55$; $p < 0.01$), less vigor ($\underline{r} = 0.46$; $p < 0.01$) and greater mood disturbance ($\underline{r} = 0.54$; $p < 0\ 01$). Wrist Actigraphy appears to be a valid and reliable *means of assessing fatigue in* cancer patients receiving chemotherapy or radiation.

Supported by D.O.D. DAMD17-96-C-6106. And IRG-18, ACS.

Abstract presented at the Multinational Association of Supportive Care in Cancer International Symposium (1998)

ASCO 1998 Annual Meeting
Abstract # 231

WRIST ACTIGRAPHY AS A MEASURE OF FATIGUE. J.T. Hickok, J.A. Roscoe, G.R. Morrow, P. Bushunow. The University of Rochester Cancer Center, Rochester, NY 14642

Nine women aged 43-70 years receiving CAF or CMF chemotherapy for breast cancer enrolled in a randomized intervention trial for fatigue were assessed on day seven of their second and fourth cycles using the Fatigue-Inertia Subscale of the Profile of Mood States (POMS-FI) and the Fatigue Symptom Checklist (FSC). These patient measures of fatigue were compared with an objective measure, the Mini-Motionlogger Actigraph (Ambulatory Monitoring, Inc., Ardsley, NY), worn on the wrist for 72 hours starting on day six of the second treatment. Six patients also had actigraphy after the fourth treatment, and one wore the Actigraph during radiation therapy following her third chemotherapy cycle. Each 24 hour period was divided into sequential intervals of time most likely spent awake and active vs time most likely spent in bed. Comparison of Actigraph measures of fatigue with subjective measures of fatigue showed that lower percent sleep during the in bed period correlated with a higher degree of fatigue as indicated by a higher mean POMS-FI score ($r = -0.54$; $p < 0.05$) whereas higher mean activity during the active awake period correlated with fewer symptoms of fatigue as shown by a lower mean total FSC score ($r = -0.50$; $p < 0.05$). These results support the use of wrist actigraphy as a valid and reliable means of assessing fatigue in ongoing studies of patients receiving chemotherapy.

Supported by grant DAMD17-96-C-6106 from DOD and IRG-18 from ACS.

THE RELATIONSHIP BETWEEN CIRCADIAN RHYTHM AND FATIGUE IN BREAST CANCER PATIENTS

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Fatigue, depression and circadian rhythm were measured one week after the second or later treatment in 76 patients receiving chemotherapy for breast cancer. We assessed fatigue by the Fatigue Symptom Checklist (FSCL) the Multidimensional Assessment of Fatigue (MAF) and the Fatigue-Inertia and Vigor subscales of the Profile of Mood States (POMS-FI and POMS-V). The Depression-Dejection subscale of the POMS was used to evaluate depression. Circadian rhythm was assessed over a 72 hour period with the Mini-Motionlogger Actigraph (Ambulatory Monitoring, Inc., Ardsley, NY). Daily patterns of sleep and activity were compared across the three-day period by autocorrelation analyses to calculate a circadian rhythm score for each patient. Higher circadian rhythm scores (i.e., a more consistent day-to-day pattern of rest and activity) were significantly related to lower fatigue reports on all measures (all $rs > .30$, all $ps < 0.01$) and also to depression ($r = .28$, $p = .02$). The relationship between fatigue and circadian rhythm remained significant or marginally significant for all measures even after controlling for depression (all partial correlation $rs > .20$, all $ps < 0.1$). These findings support a role for the physiologic process of circadian rhythm disruption in the psychological experience of fatigue in cancer patients.

Abstract and poster presented at the Society of Behavioral Medicine's Twenty-First Annual Meeting, (2000)

THE RELATIONSHIP OF CIRCADIAN RHYTHM WITH FATIGUE AND DEPRESSION IN BREAST CANCER PATIENTS

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University of Rochester Cancer Center, Rochester, NY

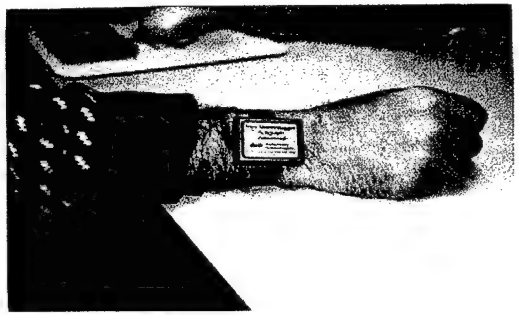
Background

While fatigue is a nearly ubiquitous symptom associated with cancer and its treatment, a definition of fatigue has gained complete acceptance[1]. Fatigue is a multidimensional concept, than tiredness, which is typically expected at a certain time of day or after activity, and which disappears after a short rest or a good night's sleep. Cancer-related fatigue is typically reported by breast cancer patients to be an unusual, distressing, and pervasive whole-body experience, unrelated to activity or exertion and is not helped by rest or sleep[2].

Fatigue is the most commonly reported treatment side effect of chemotherapy for breast cancer. Fatigue has been found to be up to seven times more prevalent in cancer patients than in the general population[3]. It is frequently reported to begin with treatment, continue through the course of chemotherapy and often persist for some time following treatment completion. In a recent study of 1048 consecutive outpatients treated solely with chemotherapy over five successive treatments, 81% of women with breast cancer reported fatigue[4]. It was the most common side effect the women experienced. The adverse effects of fatigue are frequently underestimated and thus go untreated[1,3].

Berger[5] and Mormont[6,7] used actigraphy to measure relative levels of activity in breast cancer and colorectal cancer patients. Both found a negative relationship between fatigue and activity levels during the day and a positive relationship between fatigue and restless sleep at night. Mormont also found a strong reduction in activity levels of colorectal cancer patients during the day and an increase in activity levels during the night as compared with a matched group of controls. In addition, the difference between daytime and nighttime activity levels in cancer patients was less than in the matched group of controls. Furthermore, Mormont found the circadian alternation of activity and rest to be altered in the group of colorectal cancer patients but not in the control group. Mormont concluded that cancer patients may have a disruption in their activity circadian rhythm cycle.

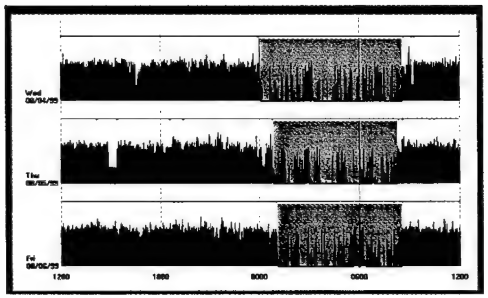
The present study extends the work of Mormont by examining the relationship between circadian rhythm and fatigue in breast cancer patients while controlling for depression. We controlled for depression, which is common among breast cancer patients, because of its strong association with both fatigue [8] and circadian rhythm disruption[9].



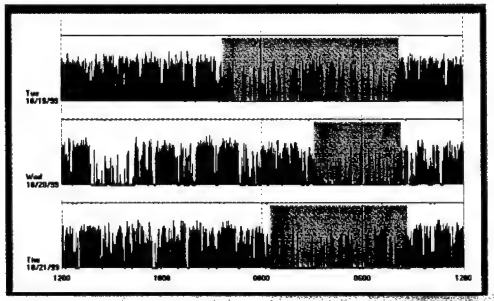
Actigraphy provides a simple non-invasive method of measuring levels of daytime and nighttime activity in patients.

Methods

Fatigue, depression and circadian rhythm were measured one week after the second or latter treatments in 78 patients receiving chemotherapy for breast cancer. We assessed fatigue by the Fatigue Symptom Checklist (FSCL), the Multidimensional Assessment of Fatigue (MAF), and the Fatigue-Inertia and Vigor Subscales of the Profile of Mood States (POMS-FI and POMS-V). The Depression-Dejection Subscale of the POMS was used to evaluate depression. Circadian rhythm was assessed over a 72-hour period with the Mini-Motionlogger Actigraph (Ambulatory Monitoring, Inc., Ardsley, NY). Daily patterns of sleep and activity were compared across the three-day period by autocorrelation analyses to calculate a circadian rhythm score for each patient.



Example of high autocorrelation. The blue shaded area indicates the overnight sleep period.



Example of low autocorrelation.

The U.S. Army Medical Research and Materiel Command under DAMD17-96-C-6106 supported this work.

Results

Higher circadian rhythm scores (i.e., a more consistent day-to-day pattern of rest and activity) were significantly related to lower fatigue reports on all measures (all rs > .30, all ps < 0.01) and also to depression (r = .28, p = .02). The relationship between fatigue and circadian rhythm remained significant or marginally significant for all measures even after controlling for depression (all partial correlation rs > .20, all ps < 0.1). These findings support a role for the physiologic process of circadian rhythm disruption in the psychological experience of fatigue in cancer patients.

Correlations Among the Fatigue, Depression and Circadian Rhythm Measures

Measure	1	2	3	4	5	6
1. Circadian Rhythm	—					
2. FSCL	-.32**	—				
3. MAF	-.31**	.68**	—			
4. POMS-FI	-.32**	.74**	.86**	—		
5. POMS-V	.34**	-.45**	-.58**	-.51**	—	
6. POMS-DD	-.28*	.57**	.46**	.54**	-.36**	—

* p < .05 ** p < .01

Conclusions

These findings support a role for the physiologic process of circadian rhythm disruption in the psychological experience of fatigue in patients receiving chemotherapy. Additional research on circadian rhythm disruption in cancer patients is recommended.

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EFFECT OF AN SSRI ANTIDEPRESSANT ON FATIGUE AND DEPRESSION IN BREAST CANCER PATIENTS TREATED WITH CHEMOTHERAPY

Gary R. Morrow, Ph.D., Joseph A. Roscoe, Ph.D., Jane T. Hickok, MD, Sara Matteson, Psy.D.
University of Rochester Cancer Center

Fatigue can significantly interfere with a cancer patient's ability to fulfil daily responsibilities and enjoy life. It commonly co-exists with depression in patients undergoing chemotherapy, suggesting that administration of an antidepressant that alleviates symptoms of depression could also reduce fatigue. We report on a double-blind clinical trial of 83 female breast cancer patients receiving at least four cycles of chemotherapy randomly assigned to receive either 20 mg of the selective serotonin re-uptake inhibitor (SSRI) paroxetine (Paxil®, SmithKline Beecham Pharmaceuticals) or an identical-appearing placebo. Patients began their study medication seven days following their first on-study treatment and continued until seven days following their fourth on-study treatment.

Questionnaires measuring fatigue (Multidimensional Assessment of Fatigue, Profile of Mood States-Fatigue/Inertia subscale and Fatigue Symptom Checklist) and depression (Profile of Mood States-Depression subscale [POMS-DD] and Center for Epidemiologic Studies-Depression [CES-D]) were completed by patients at home seven days following each treatment. Baseline (treatment 1) measures of fatigue and depression were comparable for patients in the two study groups. Repeated Measures ANOVA, after controlling for baseline measures, showed that paroxetine was more effective than placebo in reducing depression during chemotherapy, as measured by the CES-D ($p < 0.02$) and the POMS-DD ($p = 0.08$) but not in reducing fatigue (all measures, $ps > 0.8$). Results show Paxil to be effective in treating depression during cancer chemotherapy and suggest that modulation of serotonin may not be a primary mechanism of fatigue related to cancer treatment.

Supported by D.O.D. DAMD17-96-C-6106. SmithKline Beecham provided medication/matching placebo.

Abstract and poster presented at the Society of Behavioral Medicine's Twenty-Second Annual Meeting (2001)

EFFECT OF AN SSRI ANTIDEPRESSANT ON FATIGUE AND DEPRESSION IN BREAST CANCER PATIENTS TREATED WITH CHEMOTHERAPY

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University of Rochester Cancer Center, Rochester, New York

Background

Fatigue is the most commonly reported treatment side effect of chemotherapy for breast cancer. It has been found to be up to four times more prevalent in cancer patients than in the general population.[1,2] It is conceptually different from tiredness, which is typically expected at a certain time of day or after activity, and which disappears after a short rest or a good night's sleep. By contrast, fatigue is typically reported by cancer patients to be an unusual, excessive, and pervasive whole-body experience, unrelated to activity or exertion that is not helped by rest or sleep.[3] It is frequently reported to begin with treatment, continue through the course of chemotherapy and often persists for some time following treatment completion. In a study of 1048 consecutive outpatients treated solely with chemotherapy over five successive treatments, 81% of women with breast cancer reported fatigue.[2]

The adverse effects of fatigue are frequently underestimated and thus go untreated.[1,4] In addition to being pervasive, persistent, debilitating and discouraging, chemotherapy treatment-induced fatigue may have serious consequences for the breast cancer patient's quality of life and ability to actively participate in their treatment. Fatigue can affect compliance with potentially curative treatment for cancer and is a common reason given by cancer patients who refuse to enter experimental protocols.[5]

As fatigue commonly co-exists with depression, and depression is widespread in patients undergoing chemotherapy (See Table below), it is reasonable to hypothesize that administration of an antidepressant which alleviates symptoms of depression could also reduce fatigue. We provide initial data examining this hypothesis by reporting on a clinical trial of breast cancer patients who received chemotherapy and who were randomly assigned to receive either the selective serotonin re-uptake inhibitor (SSRI) paroxetine (Paxil®, SmithKline Beecham Pharmaceuticals) or an identical-appearing placebo during their treatments.

Percentage of Cancer Patients Reporting Depression* in Five Studies (N=311)

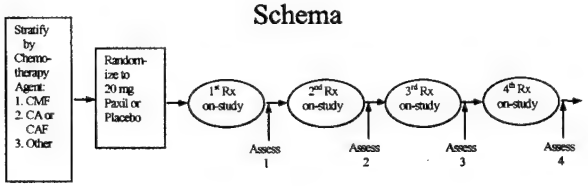
	N	Frequency
Mitchell & Glickman[6]	50	82%
Peck & Boland[7]	50	74%
Devlen et al.[8]	120	40%
Nerenz et al.[9]	61	61%
Kubricht[10]	30	56%
Mean Weighted Incidence		**58%**

* Depression assessed by structured clinical interviews using DSM-IIIR criteria.

Methods

To test the hypothesis that administering the antidepressant medication Paxil during chemotherapy treatment would lead to a reduction in patient fatigue, we conducted a randomized, double-blind, placebo-controlled clinical trial of female breast cancer patients studied over four successive chemotherapy treatments. Patients received a capsule containing 20 mg of the antidepressant Paxil or an identical looking placebo once a day during the trial (typically 9 - 12 weeks). Questionnaires measuring fatigue (Multidimensional Assessment of Fatigue [MAF]; Profile of Mood States-Fatigue/Inertia subscale [POMS-FI] and Fatigue Symptom Checklist [FSCL]) and depression (Profile of Mood States-Depression subscale [POMS-DD] and Center for Epidemiologic Studies-Depression [CES-D]) were completed by patients at home seven days following each treatment.

Schema



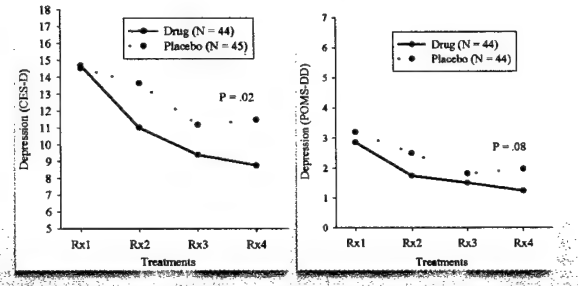
Patient Sample

One hundred twenty-two women agreed to participate in the study. We report on the 89 patients who remained on study for all four chemotherapy cycles. Patients' ages ranged from 31 - 79 (mean = 51.1). There were no significant differences between the 44 patients in the intervention group and the 45 patients in the placebo group in mean baseline measures of fatigue or depression. Using a CES-D score of 19 or greater to indicate depression, 12 patients in the placebo group and 13 in the paroxetine group were significantly depressed at baseline (28% combined).

Results

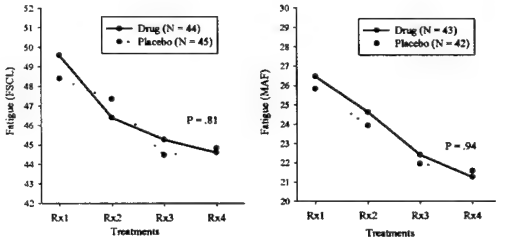
Repeated Measures ANOVA, after controlling for baseline measures, showed that paroxetine was more effective than placebo in reducing depression during chemotherapy, as measured by the CES-D ($p < 0.02$) and the POMS-DD ($p = 0.08$) but not in reducing fatigue (all measures, $ps > 0.8$).

Depression Over Time by Treatment Group



The two depression measures were highly correlated ($rs \geq .73$ at all treatments) and correlations between the first and last treatments were > .51. Analysis of variance showed that patients in the intervention group had a significant decrease in both measures of depression over time (both, $ps < .01$). The observed decrease in the control group was not statistically significant (both, $ps > .05$).

Fatigue Over Time by Treatment Group



Correlations within treatment cycles between the fatigue measures were generally in the .6 to .7 range and all inter measure correlations between the first and last treatments were > .57. While an inspection of the means (for the combined groups) showed a reduction in fatigue over time in all three measures of fatigue, this decrease was statistically significant only in respect to the MAF measure ($p < .05$). Correlation between the fatigue and depression measures ranged from .40 to .76.

Conclusions

Results show Paxil to be effective in improving symptoms of depression during cancer chemotherapy and suggest that modulation of serotonin may not be a primary mechanism of fatigue related to cancer treatment. It is possible, given the high correlations between fatigue and depression in this sample, that pharmacologic interventions for depression using drugs of a different class could have a beneficial effect on fatigue. Further study is warranted.

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ASCO 2001 Annual Meeting
Abstract #2952

CIRCADIAN RHYTHM, FATIGUE AND DEPRESSION IN BREAST CANCER PATIENTS RECEIVING CHEMOTHERAPY

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Seventy-nine female breast cancer patients naïve to chemotherapy were assessed for fatigue, depression and circadian rhythm on day seven of their second and fourth on-study chemotherapy cycle. Fatigue was measured using the Multidimensional Assessment of Fatigue (MAF), the Fatigue Symptom Checklist (FSCL) and the Profile of Mood States (POMS) fatigue/inertia (F/I) subscale. Depression was measured with the POMS depression/dejection (D/D) subscale and the Center for Epidemiological Studies Depression Scale (CES-D). Circadian rhythm was assessed over a 72 hour period with the Mini-Motionlogger Actigraph (Ambulatory Monitoring, Inc., Ardsley, NY). Daily patterns of sleep and activity were compared across the three-day period by autocorrelation analyses to calculate a circadian rhythm score for each patient, with higher scores associated with lower disruption. Comparisons of fatigue and depression with patient activity/circadian rhythm measures taken after the second cycle indicate that the measures of fatigue and depression correlated well with the measure of circadian rhythm (all $rs < -0.25$, all $ps < 0.05$). Correlations of the change scores in all of the fatigue measures and one of the depression measures from the 2^{ND} to the 4^{TH} on-study treatment were significantly related to concurrent changes in circadian rhythm. (MAF $r = -0.30$; $p = .05$; FSCL $r = -0.30$; $p < .05$; POMS F/I $r = -0.43$; $p < .01$; CES-D $r = -0.39$; $p < .01$;). These findings provide evidence that the physiologic process of circadian rhythm disruption is involved in the psychological experience of fatigue and depression in cancer patients. Supported by Award Number DAMD17-96-C-6106 from the Department of Defense.

AN SSRI ANTIDEPRESSANT REDUCED DEPRESSION BUT NOT FATIGUE IN NINETY-SIX BREAST CANCER PATIENTS

*Gary R. Morrow, Ph.D., Joseph A. Roscoe, Ph.D., Jane T. Hickok, MD, Brian Smith, MD, Raman Qazi, MD
University of Rochester Cancer Center, Rochester, NY, USA

Fatigue commonly co-exists with depression in patients undergoing chemotherapy, suggesting that administration of an antidepressant that alleviates symptoms of depression could also reduce fatigue. We report on a double-blind clinical trial of 96 breast cancer patients who received at least three cycles of chemotherapy and who were randomly assigned to receive either 20 mg of the selective serotonin re-uptake inhibitor (SSRI) paroxetine (Paxil®) or an identical-appearing placebo. Patients began their study medication seven days following their first on-study treatment and continued until seven days following their fourth on-study treatment.

The Multidimensional Assessment of Fatigue (MAF), the Fatigue Symptom Checklist (FSCL), the Profile of Mood States (POMS) and Center for Epidemiologic Studies-Depression [CES-D]) were completed by patients at home seven days following each treatment to assess symptom severity. Baseline (treatment 1) measures were comparable for patients in the two study groups. Analysis of covariance on depression, with the mean score of the CES-D from the 3rd and 4th treatments as the dependent variable, controlling for baseline CES-D, showed that paroxetine was more effective than placebo in reducing depression during chemotherapy ($p = .03$) (estimated marginal means: placebo = 12.5, SE = .84; Paxil = 9.7, SE = .91). Similarly structured analyses, however, showed that treatment condition was not related to changes in fatigue or total mood (all ps > .5) (estimated marginal means: MAF, placebo = 23.3, SE = 1.2; Paxil = 22.3, SE = 1.3; FSCL, placebo = 48.1, SE = 1.7; Paxil = 46.6, SE = 1.8; POMS, placebo = 9.4, SE = 1.6; Paxil = 8.1, SE = 1.7).

Results show Paxil to be effective in treating depression during cancer chemotherapy and suggest that modulation of serotonin may not be a primary mechanism of fatigue related to cancer treatment.

Supported by D.O.D. DAMD17-96-C-6106. SmithKline Beecham provided medication/matching placebo.

Abstract accepted for presentation at the Multinational Association of Supportive Care in Cancer International Symposium (2001)

Temporal interrelationships among fatigue, circadian rhythms and depression in breast cancer patients undergoing chemotherapy treatment.

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Fatigue is a pervasive and frequently debilitating side effect of chemotherapy treatments [34, 41, 44]. Fatigue related to cancer and its treatments differs from that induced by other causes, such as sleep disturbance and exertion, as the latter are typically alleviated by a period of rest. Fatigue in cancer patients is frequently reported to be an unusual, excessive, and pervasive whole-body experience, unrelated to activity or exertion that is not helped by rest or sleep [24].

In addition to being pervasive, persistent, debilitating, and discouraging, treatment-induced fatigue may have serious consequences for the cancer patient's quality of life and ability to actively comply with potentially curative treatment [11, 23, 40]. It is a common reason given by cancer patients who refuse to enter experimental protocols [6]. Fatigue can significantly reduce a patient's ability to perform activities of daily living. It can interfere with one's capacity to sustain meaningful relationships with family and friends, participate in leisure activities, impede concentration, and diminish the ability to work [5, 10, 11]. High fatigue may also place patients into a dependent position of having to rely on others for home management, transportation, and even simple aspects of self-care activities, such as preparing food or bathing.

Circadian Alterations and Fatigue

It has been suggested that circadian rhythms, or disruption of them, play a role in fatigue related to chemotherapy [1, 39]. Circadian rhythms are endogenous, genetically based, physiological patterns that run on an approximately 24-hour cycle and modulate several biological functions, including body temperature, cortisol, melatonin and growth hormone secretion, and REM sleep [19, 28, 35, 38].

Circadian rhythms can be altered by environmental factors, such as light and dark alterations. Desynchronization of circadian rhythms results in symptoms, such as sleep disorders, trouble concentrating, irritability, depression, lightheadedness, and loss of appetite [15].

Evidence from experimental tumor models and from cancer patients shows that cancer may alter circadian rhythms [8, 17, 19, 32, 33]. For example, Mormont et al., [18] found large circadian variation in measures of serum cortisol concentrations in patients with colorectal cancer. Average peak-trough differences were significantly lower (30%) in patients with colorectal or ovarian cancer compared to healthy controls. Relatedly, Ronco and Halberg [31] found that melatonin production, which is involved in the control of sleep, is more strongly correlated with the circadian pattern in healthy individuals than in women with breast cancer.

One method of studying the relationship between circadian rhythms and fatigue is by monitoring activity levels. This may be done through the use of an actigraph, a motion-sensing device approximately the size of a wrist watch comprised of an accelerometer, a microprocessor, and 32K of retrievable memory. Actigraphy is a simple non-invasive method of measuring levels of daytime and nighttime activity and can be used to accurately estimate amounts of both day and nighttime sleep. In addition, activity patterns over several consecutive days can be analyzed using autocorrelational techniques to provide estimates of circadian rhythms [13, 37].

A negative relationship between fatigue and activity levels during the day and a positive relationship between fatigue and restless sleep at night has been found in cancer patients [1] [17]. Mormont [1] also reported a marked reduction in the general activity

levels of colorectal cancer patients during the day and an increase in activity levels during the night as compared with a matched group of controls. The difference between daytime and nighttime activity levels in cancer patients was less than in the matched group of controls. Furthermore, Mormont found the circadian rhythm of activity and rest to be altered in the group of colorectal cancer patients but not in the control group. She concluded that cancer patients might have a disruption in their activity circadian rhythm cycle.

This study examines the temporal interrelationships among fatigue, circadian rhythms, and depression in breast cancer patients undergoing treatment with chemotherapy. We examined depression as a variable of interest in its own right and also because of its strong association with fatigue [2, 4, 12, 25]. Although the nature of the relationship between these two phenomena is not fully understood, fatigue is generally believed to lead to depression more than depression results in fatigue [40]. There is substantial evidence linking depression with alterations in the circadian rhythms of various physiological parameters and activity levels [3, 9, 14, 42].

METHODS

Procedures

Data were collected as part of a double blind, placebo-controlled clinical trial examining the efficacy of an antidepressant medication in attenuating or preventing the development of fatigue in women during chemotherapy treatment for breast cancer. Patients were randomized to receive either 20 mg paroxetine (Paxil®) or an identical appearing placebo daily. Patients, anytime in their course of treatment, were potentially eligible if they

were scheduled to receive at least four additional cycles of chemotherapy without concurrent radiation therapy or interferon. Radiation therapy sandwiched between cycles of chemotherapy was allowed and counted as a treatment cycle. Changes in chemotherapy doses or regimens were also allowed. Treatment cycles were a minimum of two weeks apart. Study medication began seven days after the first on-study treatment and concluded seven days following the fourth on-study treatment. Patients taking psychotropic medication or who had a history of psychiatric or certain neurologic diagnoses were not eligible to participate.Study subjects were patients at a university medical center and two affiliated hospitals. The Institutional Review Boards of each participating institution approved the study.

Outcome Measures

Patients were assessed using the Karnofsky Performance Scale at study entry and completed measures of fatigue, depression, and overall mood following each of the four on-study chemotherapy treatments. Measures were completed at home on the 7th day after each treatment. A reminder phone call was made to patients on the day the questionnaires were to be completed. Patient activity was sampledby actigraphy andmotion was recorded six times a minute during the 6th, 7th and 8th days following the second and fourth on-study treatments with the Mini-Motionlogger Actigraph (Ambulatory Monitoring, Inc., Ardsley, New York). The motion data were analyzed using the Cole/Kripke sleep scoring algorithm [7] to provide an assessment of sleep. Software supplied by the manufacturer was used to determine the mean activity level during the wake cycle and to generate a circadian rhythm score for each assessment.

Two measures were used to assess fatigue: the Fatigue Symptom Checklist (FSCL) [26, 45] and the Multidimensional Assessment of Fatigue (MAF) [36]. The FSCL consists of 30 items in three subscales: drowsiness and dullness, difficulty of concentration, and projection of physical impairment. The presence and intensity of each item is indicated on a five-point scale with "1" = "Absence of" and "5" = "A great deal." The revised MAF [36] measures four dimensions of fatigue (severity, distress, interference with activities of daily living, and timing) through 16 questions, 14 of which are visual analog scales anchored by "1" = "Not at all" and "10" = "A great deal."

Depression was assessed using the Center for Epidemiological Studies Depression Scale (CES-D) [27] and the Hamilton Depression Inventory (HDI) [29]. The CES-D is a 20-item depression scale in a format similar to that of the Beck Depression Inventory, but with less emphasis on physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. Patients indicated how often they had experienced 20 symptoms with "1" = Rarely or none of the time" and "4" = "Most or all of the time." The HDI comprises 23 items (or symptoms) that are evaluated using 38 questions. This is a recently developed paper and pencil version of the Hamilton Depression Rating Scale (HDRS) and measures the severity of symptoms of depression over the previous two weeks. Validity and reliability were confirmed in a sample of 357 adults [30].

Overall mood was assessed with the monopolar Profile of Mood States (POMS) Short Form. The POMS Short Form consists of 30 adjectives in six subscales: depression/dejection, fatigue/inertia, tension/anxiety, vigor, anger/hostility, and confusion/bewilderment. It screens for general affective signs of mood disturbance.

Subjects rate the 30 adjectives (on a five-point scale with "1" = "Not at all" and '5" = Extremely) to describe their moods over the past week. It has been shown to be internally consistent, reliable, and valid in a number of psychometric studies [16].

Sample Characteristics

One hundred twenty-two women and two men consented to participate in the study. Twenty-two (18%) patients withdrew from the study prior to data collection from the second treatment. Ninety-one of the remaining 102 patients provided evaluable actigraph data following the second on-study treatment. Despite careful instruction on the importance of wearing the actigraph for three days, 12 patients did not do so for a variety of reasons. Overall, actigraphy data were available from 78 evaluable patients, or 73% of those giving consent. All 78 patients werefemale.

The mean age of the sample of 78 women was 51.7 years (range = 34 to 79). At the time of the initial circadian rhythm assessment following the second on-study treatment, 29 (37%) patients were receiving CMF therapy, 35 (45%) patients were receiving chemotherapy regimens containing cyclophosphamide and doxorubicin with or without fluorouracil, and 14 (18%) patients were receiving other chemotherapy regimens. Thirty-eight (49%) of these patients were assigned to the paroxetine condition and the remaining 40 (51%) to the placebo condition. The patients were all mobile and had an average Karnofsky Performance Status of 90 (range = 70 to 100).

Three variables were derived from the actigraph at each of the two assessment points. The first variable, **Circadian Rhythm,** is a measure of similarity or dissimilarity

of rest and activity patterns across the three measurement days. It was calculated using the autocorrelation feature of the Action-3 analysis program (Ambulatory Monitoring, Inc., Ardsley, New York). The autocorrelation coefficient can in theory range between –1 and 1 (see Mormont [20] for a description of how autocorrelation is calculated). The other two variables were generated by the companys' companion analysis program, Action-W, which separates the day into an "up" or out-of-bed portion of the day and a "down" or in-bed portion. The resulting **Mean Activity** and **Percent Sleep** variables are, respectively, the average activity level and proportion of time resting or sleeping in the "up" portion of the day.

Insert Figure 1 here

Results

The autocorrelation coefficients following the second chemotherapy treatment had a normal distribution and ranged from 0.16 to 0.85 (median = .56, mean = .57). For comparison purposes, autocorrelation coefficients from ranged from -0.06 to 0.77 (median = 0.42) in the 192 patients with metastatic colorectal cancer reported on by Mormont [20]. Figure 1 provides examples of high and low circadian rhythm patterns. Each line in the figures represents 24 hours of data with greater density of markings indicating greater frequency of wrist movements. The gray shaded areas delineate the "down" or major in bed portion of the day and the underlined areas indicate data scored as sleep. The patients whose data is shown in the upper graph in Figure 1 had an autocorrelation score of 0.85 and had 0.1% of her "up" time scored as sleep. The corresponding numbers for the lower graph are 0.25 and 19.4%, respectively.

Circadian rhythm and mean activity following the second chemotherapy treatment were significantly correlated with baseline Karnofsky Performance Status (KPS), both $\underline{r}s = .29$, both $\underline{p}s < 0.02$. The relation between KPS and percent sleep was not significant, $r = -.17$, $\underline{p} = .15$. Patient age was not significantly correlated with any of the actigraph measures, all $\underline{p}s > .05$, nor was randomization to paroxetine versus placebo, all $\underline{p}s > .05$.

Partial correlational analyses, after controlling for KPS, showed that the three actigraph measures (circadian rhythm, percent sleep, and mean activity) were significantly correlated with each other, and for the most part, significantly correlated with the five paper and pencil questionnaires measuring fatigue, mood and depression (Table 1). The measures of fatigue, mood, and depression were also strongly correlated with one another as has been found in previous studies of cancer patients undergoing treatment, confirming their co-existence in patients in this sample.

Insert Table 1 here

We were able to obtain three-day actigraph measures from 45 (58%) of the 78 patients following their fourth on-study treatment and calculated simple change scores on the eight study variables by subtracting the time 2 measurements from the time 4 measurements. Changes over time in the actigraphy measures were, in general, significantly correlated with changes in fatigue, mood, and depression (Table 2). Change scores in the measures of fatigue, mood, and depression over time were strongly correlated with one another. As in the baseline measures, changes in the actigraphy measures were not related to whether or not patients received paroxetine, all $\underline{p}s > .05$.

Insert Table 2 here

A median split was used to divide patients based upon their circadian rhythm score following their second on-study treatment. Patients in the group with the higher circadian rhythm scores (i.e., a more consistent day-to-day pattern of rest and activity) reported significantly less fatigue, mood disturbance, and depression compared to patients with less consistent patterns, all ps < .02. (Figure 2). Change scores in circadian rhythm were similarly analyzed. The 23 patients with the most improved circadian rhythm patterns reported a positive change in fatigue and mood while the remaining 22 patients experienced a negative change in these areas, all ps < .05. In addition, while patients in both groups had a mean improvement in depression, the amount of positive change was greater in the former group compared to the latter. This difference approached conventional levels of significance when measured by the CES-D, $p > .06$, but was not statistically significant when measured by the HDI, $p = 0.19$ (Figure 3).

Insert Figures 2 & 3 here

Discussion

These findings provide evidence that the physiologic process of circadian rhythm disruption is involved in the psychological experience of fatigue and depression in cancer patients. Correlation results, even significant correlations do not provide further information on the nature of that potential association.

Results show that data from actigraphy methodology may prove valuable in the

study of cancer related fatigue. Wrist Actigraphy appears to be a valid and reliable means of assessing fatigue in cancer patients receiving chemotherapy. The finding that there were changes over the course of treatment indicates that this methodology can be a sensitive response to chemotherapy that might provide an alternative frame of reference for study. We found significant correlations between the three actigraph measures (circadian rhythm, proportion of sleep in the "up" period, and mean activity in the "up" period) and patients' self-assessment of fatigue. In addition, changes in the actigraph measures over time were significantly correlated with changes in these self-reports.

Further studies comparing the actigraphy assessment of circadian changes based on motion with other circadian systems such as temperature and cortisol would aid understanding of the involvement of circadian changes in cancer and its treatment as well as provide additional, valuable validity data on this potential assessment methodology.

The significant, consistent interrelationships among measures of fatigue, sleep depression and circadian activity in cancer patients supports speculation that they all may share some common potential mechanism that governs their development or expression. Central serotonin has been shown to be involved in sleep and depression. We have speculated on the role of 5-HT in fatigue; although recent data [22] have cast doubt on a strong causal association. It is intriguing to note that while serotonergic pathways and the neurotransmitter 5-HT (5-hydroxytryptamine) has been associated with the regulation of circadian rhythm [28], receiving or not receiving an SSRI antidepressant was not related to circadian patterns in this study. Receipt of 20 mg paroxetine daily versus placebo was not related to baseline circadian rhythm patterns nor to changes over time in rest and activity patterns.

The changes in circadian rhythm were noted relatively early in the chemotherapy treatment cycles. It is possible that an early measure of the degree of a cancer patient's circadian disruption may have predictive value in the early identification of patients at elevated risk for the development of fatigue or mood disturbance during chemotherapy treatment. If further study shows such predictive value, the simple assessment by actigraphy might help target patients for whom early intervention with either (or both) psychological and pharmacological treatment might be appropriate. For example, there is some evidence that cognitive-behavioral therapy may help reduce fatigue in cancer patients. As this treatment is labor intensive, the ability to identify patients for whom it might have maximum benefits would be quite cost effective.

There is not a well-developed literature on the effects of chemotherapy treatment on sleep. The very strong relationship found between circadian rhythm and sleep suggests potentially fruitful avenues for future investigation of how these two variables may interrelate and also relate to fatigue and depression. Such studies might help better formulate a mechanistic model that reasonable speculates on potential interrelationships among sleep, fatigue, depression and circadian rhythm in cancer patients [21, 43].

Table 1. Partial Correlations of Study Measures from Patient's 2nd On-Study Treatment, Controlling for Baseline Performance Status[a]

Measure	1	2	3	4	5	6	7	8
1. Circadian Rhythm[b]	---							
2. Mean Activity[c]	.65**	---						
3. Percent Sleep[d]	-.52**	-.82**	---					
4. FSCL	-.26*	-.21	. 27*	---				
5. MAF	-.27*	-.23*	.30**	.63**	---			
6. CESD	-.32**	-.30**	.40**	.63**	.66**	---		
7. HDI	-.25*	-.25*	.31**	.66**	.68**	.75**	---	
8. POMS	-.37**	-.26*	.36**	.78**	.75**	.83**	.74**	---

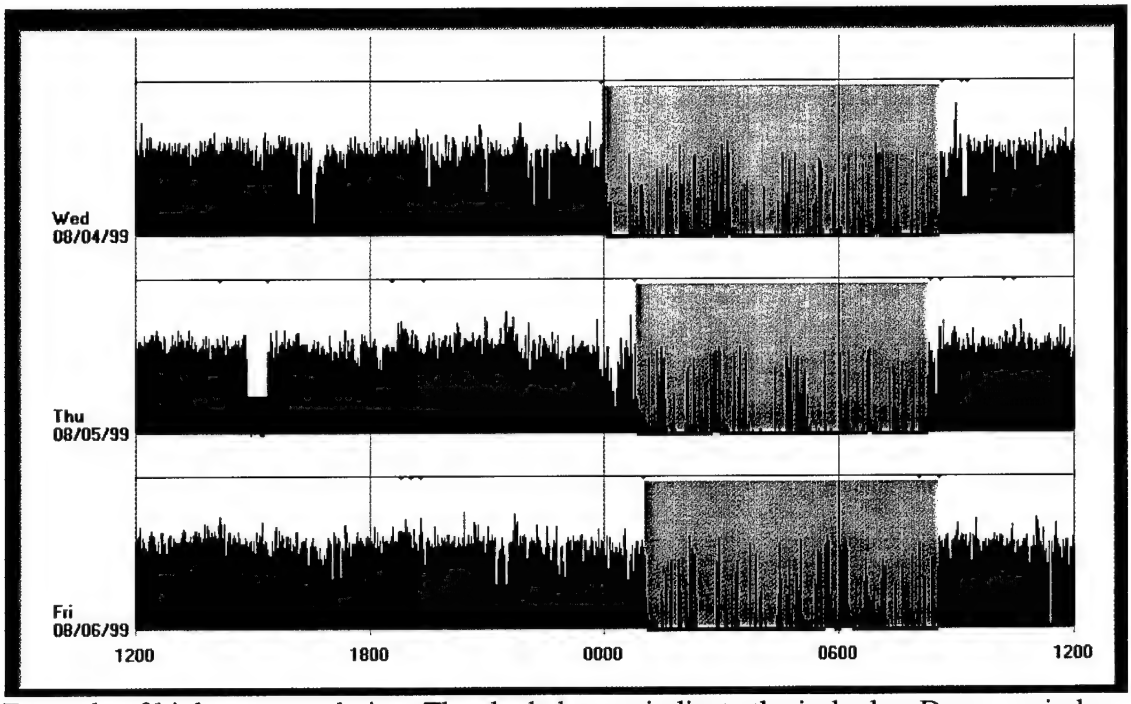
Notes: N = 76-78; [a] measured on Karnofsky Performace Scale; [b] actigraph measurement of autocorrelation [c] actigraph measurement of daytime activity level; [d] actigraph measurement of daytime nap and rest periods.
* $p < .05$, ** $p < .01$

Table 2. Correlations of Change Scores[a] (from 2nd On-Study Treatment to 4th On-Study Treatment)

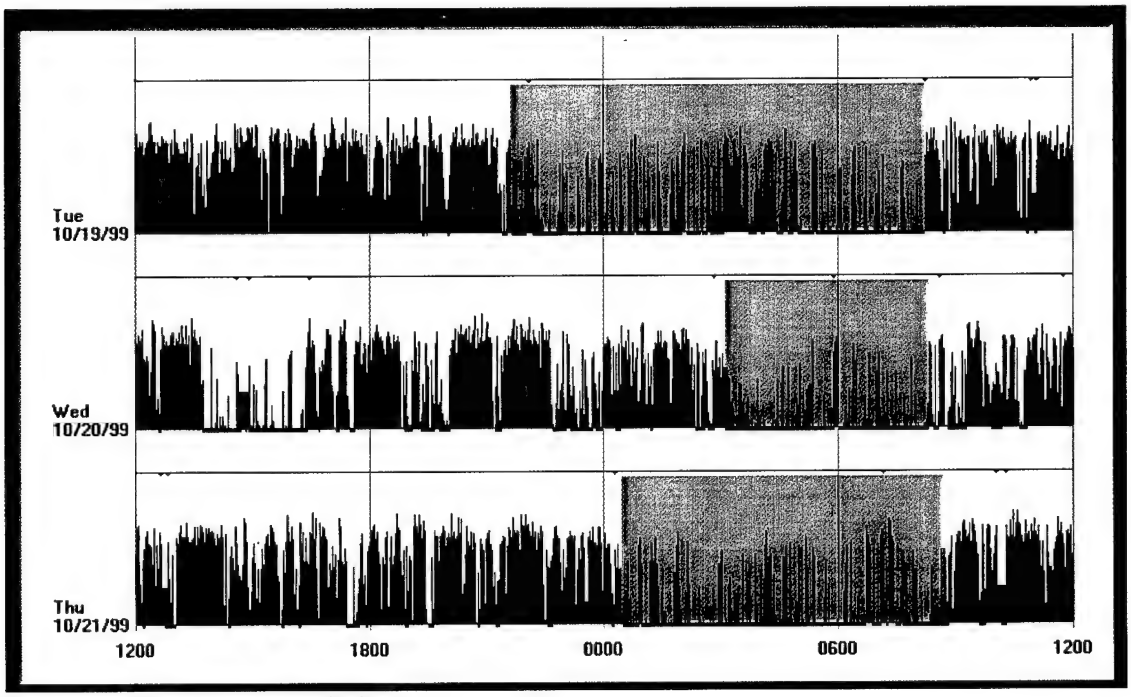
Measure	1	2	3	4	5	6	7	8
1. Circadian Rhythm	---							
2. Mean Activity	.65**	---						
3. Percent Sleep	-.63**	-.82**	---					
4. FSCL	-.30*	-.42**	. 43**	---				
5. MAF	-.31*	-.23	.20	.57**	---			
6. CESD	-.39**	-.59**	.58**	.63**	.55**	---		
7. HDI	-.34*	-.34*	.32*	.42**	.64**	.60**	---	
8. POMS	-.40**	-.41**	.36*	.75**	.73**	.79**	.61**	---

Note: N = 39-45; [a] change score calculated by subtracting time 2 measurement from time 4 measurement; therefore, a positive circadian rhythm value indicates a more regular rhythm and a positive symptom score means greater symptom severity.
* $p < .05$, ** $p < .01$

Figure1. Examples of Actigraph Activity Patterns

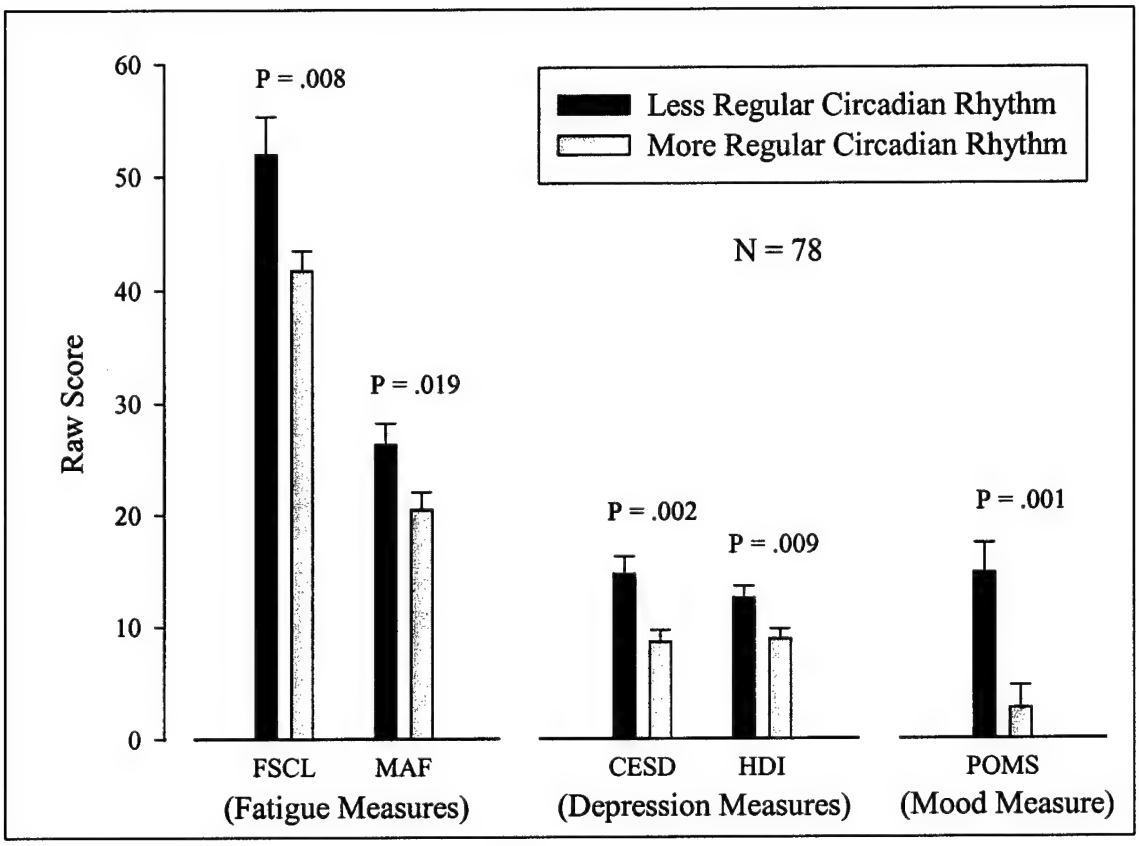


Example of high autocorrelation. The shaded areas indicate the in-bed or Down periods.



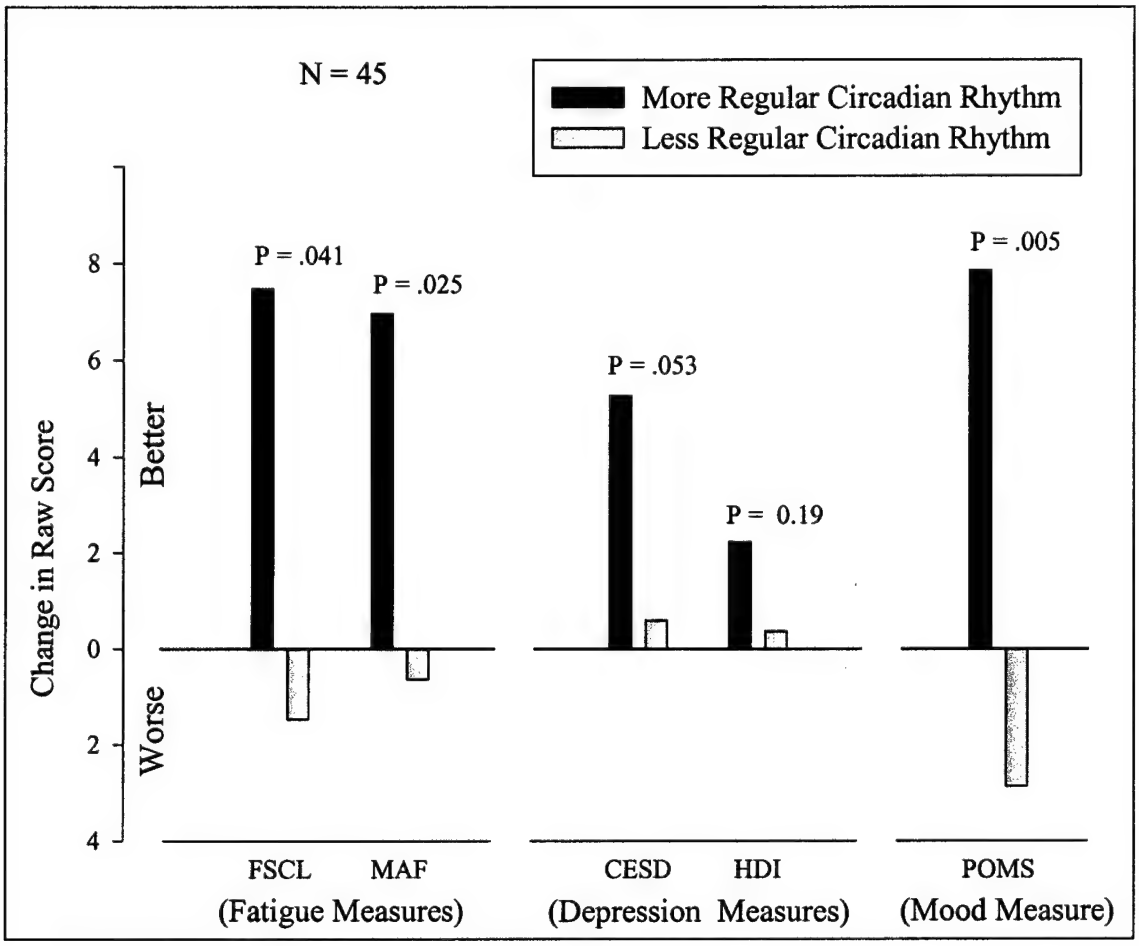
Example of low autocorrelation.

Figure 2. Comparison of Fatigue, Depression and Mood by Median Split on Circadian Rhythm Measure One Week Following Patients' Second On-Study Treatment



Note: Higher scores indicate greater symptom severity.

Figure 3. Comparison of Change in Fatigue, Depression and Mood from Patients' Second to Fourth On-Study Treatments by Median Split on Change in Circadian Rhythm



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